Amendment to the Drawings:

The attached sheet of drawings includes changes to Fig. 9. This sheet, replaces the original sheet including Fig. 9.

Attachment: Replacement Sheet
Annotated Sheet Showing Changes

REMARKS/ARGUMENTS

These Amendments and Remarks are in response to the Office Action issued September 18, 2008. Reconsideration of this application is respectfully requested.

No new matter has been introduced as a result of the amendments to the claims, the specification and the drawings.

By the amendments, Applicants do not acquiesce to the propriety of any of the Office's rejections and do not disclaim any subject matter to which Applicants are entitled. *Cf. Warner Jenkinson Co. v. Hilton-Davis Chem. Co.*, 41 U.S.P.Q.2d 1865 (U.S. 1997). Applicants reserve the right to file continuing or divisional applications to any claims amended, cancelled or withdrawn for any reason.

Withdrawn Rejections

The Applicants note with appreciation the Examiner's withdrawal of the rejections under 35 U.S.C. §103(a). Office Action mailed September 18, 2008 ("OA"), pages 2-3.

In the Claims

Claims 1-10, 12-17 and 20-29 are pending in this application. Claims 3-6 and 14-17 have been withdrawn as the result of an earlier restriction requirement without prejudice to Applicants' right to pursue the subject matter of the withdrawn claims in one or more related applications. Claims 11, 18 and 19 were previously cancelled.

Claim 31 has been amended to incorporate the sequence identifier for LAA, SEQ ID NO:34.

In the Drawings

Figure 9 has been amended to correct a typographical error and to include the sequence identifier for LAA, SEQ ID NO:34. A replacement sheet for Figure 9 has been included. The fragment of A36R included in LAA comprises amino acids 57-184. Support for this amendment can be found in the specification in paragraph [0051].

In the Specification

Paragraph [0049] of the specification was amended to correct two typographical errors. The 5' primer added "an" AflII site. Also, the 3' primer changed the K at position 177, not position 176 as originally written. Support for this amendment can be found in Figure 3.

Paragraph [0051] of the specification has been amended to correct two typographical errors and to include the sequence identifier for LAA. The fragment of M1R included in LAA is from residue 1 to 186. Support for this amendment can be found in Figure 9. In the last line of paragraph [0051], "LAA" was mistakenly typed as "LM."

Objections

Claim 31 was objected to because the sequence listing does not have a sequence identifier for polyprotein LAA. OA, page 3.

The amino acid sequence of polyprotein LAA has been assigned SEQ ID NO: 34. Claim 31 and paragraph [0051] of the specification have been amended to incorporate this sequence identifier.

A Supplemental Sequence Listing is filed herewith including SEQ ID NO: 34.

Rejections Under 35 U.S.C. §103

1. Claims 1-2, 7-8, 10, 20, 22 and 27-30 have been rejected under 35 USC §103(a) as being unpatentable over Hooper *et al.* (Virology, 2000, Vol. 266, pgs. 329-339; hereinafter "Hooper") in view of Hooper *et al.* (US2002/0009447 A1; hereinafter "Hooper Pub"). OA, page 4. Applicants respectfully disagree.

To maintain a proper rejection under 35 U.S.C. §103, the Office must meet four conditions to establish a *prima facie* case of obviousness. First, the Office must show that the prior art suggested to those of ordinary skill in the art that they should make the claimed composition or device or carry out the claimed process. Second, the Office must show that the prior art would have provided one of ordinary skill in the art with a

reasonable expectation of success. Both the suggestion and the reasonable expectation of success must be adequately founded in the prior art and not in an applicant's disclosure. Third, the prior art must teach or suggest all the claim limitations. *In re Vaeck,* 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). Fourth, if an obviousness rejection is based on some combination of prior art references, the Office must show a suggestion, teaching, or motivation to combine the prior art references ("the TSM test"). *In re Dembiczak,* 50 U.S.P.Q.2d 1614, 1617 (Fed. Cir. 1999). Following *KSR Int'l Co. v. Teleflex, Inc.*, this fourth prong of the *prima facie* obviousness analysis must not be applied in a rigid or formulaic way such that it becomes inconsistent with the more flexible approach of *Graham v. John Deere*, 383 U.S. 1, 17-18 (1966); 127 S. Ct. 1727 (2007). It must still be applied, however, as the TSM test captures the important insight that "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *Id.* at 1741 (citing *United States v. Adams*, 383 U.S. 39, 50-52 (1966)).

A. The Instant Claims

The instant claims are drawn to polyproteins comprising external immunogens of membrane associated proteins of variola major or immunologically cross-reactive poxviruses (claims 1, 2, 7-10, 23-27, 29 and 31) or immunogenic compositions comprising complexes of polypeptides wherein each polypeptide comprises an external immunogen of a membrane associated protein of variola major or immunologically cross-reactive poxviruses (claims 20-22, 28 and 30).

B. The Prior Art

i. Hooper

Hooper teaches DNA vaccines comprising the vaccinia virus L1R and A33R genes which have been used to vaccinate mice against a lethal challenge with vaccinia. The DNA vaccine of Hooper comprises the A33R and L1R genes individually cloned into naked DNA expression vectors to yield constructs pWRG/A33R and pWRG/L1R.

The immunogens taught by Hooper include DNA constructs WRG/A33R and/or pWRG/L1R.

ii. Hooper Pub

Hooper Pub teaches vaccinia-specific monoclonal antibodies raised against vaccinia gene products.

C. The prior art does not teach or suggest all the claim limitations.

Instant claims 1, 2, 7-8, 10, and 27-29 are drawn to polyproteins. Neither Hooper nor Hooper Pub, individually or in combination, teach or suggest polyproteins, which are defined in the instant specification as "more than one protein, or polypeptide, made as a result of a single transcriptional event that has not been cleaved into individual proteins, or polypeptide, chains." Specification, paragraph [0027]. Therefore claims 1, 2, 7-8, 10, and 27-29 are not obvious in view of Hooper and Hooper Pub.

Instant claims 20, 22 and 30 are drawn to immunogenic compositions comprising complexes of polypeptides wherein each polypeptide comprises an external immunogen of a membrane associated protein of variola major or immunologically cross-reactive poxviruses. Hooper teaches only naked DNA vaccines and does not teach or suggest complexes of proteins or polypeptides. Hooper Pub does not cure the deficiencies of Hooper in that it also does not teach immunogenic compositions comprising complexes of polypeptides.

D. The prior art teaches away from the claimed compositions.

Hooper teaches that when plasmids containing the L1R and A33R vaccinia genes are loaded onto the same gold particle, and therefore expressed in the same cell, immunization is ineffective for the generation of neutralizing antibodies or protection from viral challenge. Hooper, abstract. Therefore, Hooper, when taken in its entirety, teaches away from the claimed invention, a polyprotein or a complex of polypeptides, for use as an immunogen against vaccinia virus. "A prior art reference must be considered in its entirety, i.e., as a whole, including portions which would lead away

from the claimed invention." *W.L. Gore & Associates, Inc. V. Garlock, Inc.* 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984).

The Office asserts

> [i]t would have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to recognize the synergy of antibodies against other proteins. The person of ordinary skill in the art would have been motivated to make that connection because Hooper Pub teaches homologs from other poxvirus can be used as immunogens to produce monoclonal antibodies, which would most likely be protective since homologs in other poxviruses have high identity with the vaccinia virus proteins, and reasonably would have expected success because of the teachings of Hooper and Hooper Pub.

OA, page 6. The Office makes no assertions that Hooper and Hooper Pub disclose all the limitations of the pending claims and therefore the Office has not made a *prima facie* case of obviousness over Hooper and Hooper Pub.

Applicants respectfully submit that Hooper and Hooper Pub, either singly or in combination, do not teach or suggest each and every element of claims 1-2, 7-8, 10, 20, 22 and 27-30, namely polyproteins or protein complexes comprising external immunogens of at least two membrane-associated proteins of variola major or immunologically cross-reactive poxviruses. Furthermore, the prior art teaches away from the claimed compositions. For each of these reasons, the Office has not established the *prima facie* obviousness of claims 1-2, 7-8, 10, 20, 22 and 27-30 over Hooper in view of Hooper Pub.

2. Claim 21 has been rejected under 35 USC §103(a) as being unpatentable over Hooper in view of Hooper Pub as applied to claims 1-2, 7-8, 10, 20, 22 and 27-30, and further in view of Curiel *et al*. (6,274,332; hereinafter "Curiel"). Applicants respectfully disagree.

Claim 21 recites an immunogenic composition comprising a complex of polypeptides wherein each polypeptide comprises an external immunogen of a membrane-associated protein of variola major or immunologically cross-reactive poxviruses, wherein each of the external immunogens comprises a portion of the

membrane-associated protein comprising the external epitopes, wherein the complex is not an entire virus and wherein the polypeptides are biotinylated and the complex is formed by the addition of avidin or streptavidin.

Hooper and Hooper Pub have been discussed *supra*. As asserted *supra* with regard to claims 1-2, 7-8, 10, 20, 22 and 27-30, the combination of Hooper and Hooper Pub do not render claim 21 *prima facie* obvious.

Curiel teaches viral conjugates wherein the virus and a nucleic acid binding domain are bound by a biotin-streptavidin bridge. Curiel does not teach or suggest a polyprotein and therefore does not cure the deficiencies of Hooper and Hooper Pub.

Applicants respectfully submit that Hooper, Hooper Pub and Curiel, either singly or in combination, do not teach or suggest each and every element of claim 21, namely protein complexes comprising external immunogens of at least two membrane-associated proteins of variola major or immunologically cross-reactive poxviruses wherein the polypeptides are biotinylated and the complex is formed by the addition of streptavidin. For each of these reasons, the Office has not established the *prima facie* obviousness of claim 21 over Hooper in view of Hooper Pub and further in view of Curiel.

3. Claims 23-26 have been rejected under 35 USC §103(a) as being unpatentable over Hooper as applied to claims 1-2, 7-8, 10, 20, 22 and 27-20 and further in view of Newton *et al*. (Biochemistry, 1996, Vol. 35, pgs. 545-553; hereinafter "Newton"). Applicants respectfully disagree.

Claim 23 recites a polyprotein comprising external immunogens of at least two membrane-associated proteins of variola major or immunologically cross-reactive poxviruses wherein the individual proteins are joined through a linker-spacer peptide and wherein each of the external immunogens comprises a portion of the membrane-associated protein comprising the external epitopes.

Hooper and Hooper Pub have been discussed *supra*. As asserted *supra* with regard to claims 1-2, 7-8, 10, 20, 22 and 27-30, the combination of Hooper and Hooper Pub do not render claims 23-26 *prima facie* obvious.

Newton teaches linkers to link peptides wherein the linkers include a $(GGGGS)_3$ linker. Newton also teaches affinity tags. Newton does not teach or suggest a polyprotein and therefore does not cure the deficiencies of Hooper and Hooper Pub.

Applicants respectfully submit that Hooper, Hooper Pub and Newton, either singly or in combination, do not teach or suggest each and every element of claims 23-26, namely polyproteins comprising external immunogens of at least two membrane-associated proteins of variola major or immunologically cross-reactive poxviruses. Furthermore, the prior art teaches away from the claimed invention. For each of these reasons, the Office has not established the *prima facie* obviousness of claims 23-26 over Hooper in view of Hooper Pub and further in view of Newton.

Allowed Claims

Claims 9 and 31 are asserted to be free from prior art as stated in the Office Action. OA, page 8.

CONCLUSION

In light of the remarks presented herein, Applicants respectfully assert that the presently pending claims are in condition for allowance and request that a timely Notice of Allowance be issued in this case.

The Commissioner is authorized to charge any fee which may be required in connection with this Amendment to deposit account No. 50-3207.

Respectfully submitted,

Dated: December 18, 2008

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